(12)特許協力条約に基づいて公開された国際出願

(19) 世界知的所有権機関
国際事務局

(43) 国際公開日
2002 年1 月3 日 (03.01.2002)

PCT

(10) 国際公開番号
WO 02/00259 A1

(51) 国際特許分類[7]: A61K 45/00, 31/496, 31/495, A61P 25/24, 25/22, C07D 295/12, 239/42, 215/12, 307/81, 209/14, 333/20, 311/80, 261/20, 211/44, 211/70, 295/06, 295/02, 295/08, 295/14, 211/20, 211/22

(21) 国際出願番号: PCT/JP01/05524

(22) 国際出願日: 2001 年6 月27 日 (27.06.2001)

(25) 国際出願の言語: 日本語

(26) 国際公開の言語: 日本語

(30) 優先権データ:
特願2000-192856 2000 年6 月27 日 (27.06.2000) JP

(71) 出願人 (米国を除く全ての指定国について): 大正製薬株式会社 (TAISHO PHARMACEUTICAL CO., LTD.) [JP/JP]; 〒170-8633 東京都豊島区高田3丁目24番1号 Tokyo (JP).

(72) 発明者; および
(75) 発明者/出願人 (米国についてのみ): 中里篤郎 (NAKAZATO, Atsuro) [JP/JP]. 茶木茂之 (CHAKI, Shigeyuki) [JP/JP]. 大久保武利 (OKUBO, Taketoshi) [JP/JP]. 小川伸一 (OGAWA, Shin-ichi) [JP/JP]. 石井孝明 (ISHII, Takaaki) [JP/JP]; 〒170-8633 東京都豊島区高田3丁目24番1号 大正製薬株式会社内 Tokyo (JP).

(74) 代理人: 北川富造 (KITAGAWA, Tomizo); 〒170-8633 東京都豊島区高田3丁目24番1号 大正製薬株式会社特許部 Tokyo (JP).

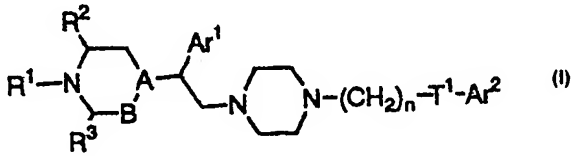
(81) 指定国 (国内): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) 指定国 (広域): ARIPO 特許 (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), ユーラシア特許 (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), ヨーロッパ特許 (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI 特許 (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

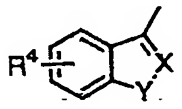
[続葉有]

(54) Title: REMEDIAL AGENT FOR ANXIETY NEUROSIS OR DEPRESSION AND PIPERAZINE DERIVATIVE

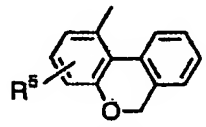
(54) 発明の名称: 不安神経症又はうつ症治療薬、及びピペラジン誘導体



(I)



(a)



(b)

(57) Abstract: A remedy for anxiety neurosis or depression which contains an MC_4 receptor antagonist as the active ingredient; and a piperazine derivative represented by the formula [I] or a pharmaceutically acceptable salt thereof, wherein Ar^1 represents (un)substituted phenyl, etc.; Ar^2 represents (un)substituted naphthyl, quinolyl, a group represented by the formula [a] (wherein R^4 is hydrogen or halogeno; and X-Y is CH-NH, CH-O, CH-S, or N-O), or a group represented by the formula [b] (wherein R^5 is hydrogen, hydroxy, or C_{1-10} alkoxy); R^1 represents hydrogen, C_{1-10} alkyl, etc.; R^2 and R^3 are the same or different and each is hydrogen or C_{1-10} alkyl; A-B represents $N-CH_2$, $CH-CH_2$, $C(OH)-CH_2$, or C=CH; T^1 represents a single bond, -O-, etc.; and n is an integer of 1 to 10.

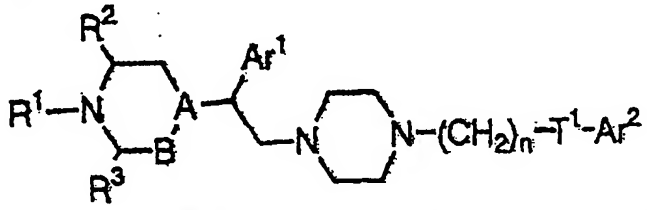
[続葉有]

WO 02/00259 A1

添付公開書類:
— 国際調査報告書

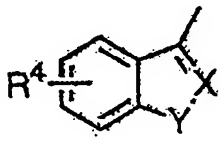
(57) 要約:

ＭＣ4受容体アンタゴニストを有効成分とする不安神経症又はうつ症治療薬、及び式[1]

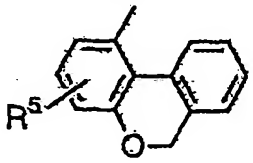


[1]

[式中、Ａｒ1は（置換））フェニル基等、Ａｒ2は（置換））ナフチル基、キノリル基、式



(式中、Ｒ4は水素原子又はハロゲン原子、Ｘ－ＹはCH-NH、CH-O、CH-S又はN-Oである。)で表される基又は式



(式中、Ｒ5は水素原子、水酸基又はC_{1-10}アルコキシ基である。)で表される基であり、Ｒ1は水素原子、C_{1-10}アルキル基等、Ｒ2及びＲ3は同一又は相異なって水素原子又はC_{1-10}アルキル基、Ａ－ＢはN-CH_2、CH-CH_2、C(OH)-CH_2又はC=CHであり、Ｔ1は単結合、-O-等、ｎは１～10の整数である。]で表されるピペラジン誘導体又はその医薬上許容される塩を提供する。

I, Masanori KOMATSU , a national of Japan, c/o Asamura Patent Office of 331-340, New Ohtemachi Building, 2-1, Ohtemachi-2-chome, Chiyoda-ku, Tokyo, Japan, declare that to the best of my knowledge and belief the attached is a full, true, and faithful translation into English made by me of Japanese Patent Application No. 2000-192856 .

Signed this 17th day of February , 2003 .

Masanori KOMATSU

2000-192856

[Title of Document] Patent Application

[Reference Number] 00YA-P3071

[Addressee] Commissioner

The Patent Office

[Inventor]

[Address] c/o Taisho Pharmaceutical Co., Ltd.,
24-1, Takata-3-chome, Toshima-ku,
Tokyo, Japan.

[Name] Atsuro NAKAZATO

[Inventor]

[Address] c/o Taisho Pharmaceutical Co., Ltd.,
24-1, Takata-3-chome, Toshima-ku,
Tokyo, Japan.

[Name] Shigeyuki CHAKI

[Inventor]

[Address] c/o Taisho Pharmaceutical Co., Ltd.,
24-1, Takata-3-chome, Toshima-ku,
Tokyo, Japan.

[Name] Taketoshi OKUBO

[Inventor]

[Address] c/o Taisho Pharmaceutical Co., Ltd., 24-1, Takata-3-chome, Toshima-ku, Tokyo, Japan.

[Name] Shin-ichi OGAWA

[Inventor]

[Address] c/o Taisho Pharmaceutical Co., Ltd., 24-1, Takata-3-chome, Toshima-ku, Tokyo, Japan.

[Name] Takaaki ISHII

[Applicant]

[Applicant's ID Number] 0 0 0 0 0 2 8 1 9

[Name] Taisho Pharmaceutical Co., Ltd.

[Agent]

[Agent's ID Number] 1 0 0 0 7 4 1 1 4

[Patent Attorney]

[Name] Tomizo KITAGAWA

[Telephone] 03-3985-1111

[Indication on Fee]

[Prepayment Register Number] 003551

[Amount of Payment] ¥21,000-

[List of Items Filed]

[Title of Article]	Specification	1
[Title of Article]	Drawings	1
[Title of Article]	Abstract	1
[Number of General Power]		9 7 0 3 0 5 8
[Proof: Required or not]		Yes

[Title of Document] Specification

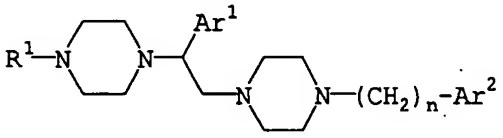
[Title of the Invention] THERAPEUTIC PREPARATION FOR ANXIETY NEUROSIS OR DEPRESSION, AND PIPERAZINE

[Scope of Claim for a Patent]

[Claim 1] A therapeutic preparation for anxiety neurosis or depression which comprises a MC_4 receptor antagonist as an effective ingredient.

[Claim 2] The therapeutic preparation for anxiety neurosis or depression according to Claim 1 wherein the MC_4 receptor antagonist is a piperazine derivative represented by Formula [1]:

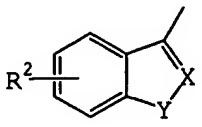
[Formula 1]



[1]

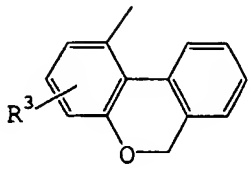
[wherein Ar^1 is a substituted or unsubstituted phenyl group, or a substituted or unsubstituted naphthyl group; Ar^2 is a substituted or unsubstituted naphthyl group, a quinolyl group, a group represented by the formula:

[Formula 2]



(wherein R^2 is a hydrogen atom or a halogen atom; and X-Y is C-NH, C-O, C-S or N-O) or a group represented by the formula:

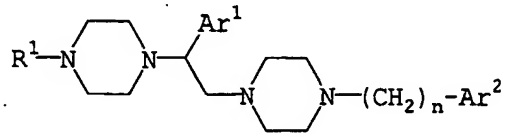
[Formula 3]



(wherein R^3 is a hydrogen atom, a hydroxyl group or a C_{1-10} alkoxy group); R^1 is a hydrogen atom, a C_{1-10} alkyl group, a C_{3-10} alkenyl group, a phenyl group, a pyrimidin-2-yl group or an amidyl group; and n is an integer of from 1 to 10], or a pharmaceutically acceptable salt thereof.

[Claim 3] A piperazine derivative represented by Formula [1]:

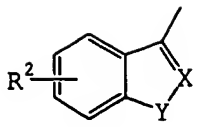
[Formula 4]



[1]

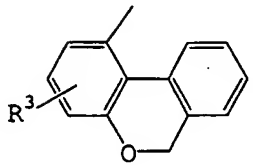
[wherein Ar^1 is a substituted or unsubstituted phenyl group, or a substituted or unsubstituted naphthyl group; Ar^2 is a substituted or unsubstituted naphthyl group, a quinolyl group, a group represented by the formula:

[Formula 5]



(wherein R^2 is a hydrogen atom or a halogen atom; and X-Y is C-NH, C-O, C-S or N-O) or a group represented by the formula:

[Formula 6]

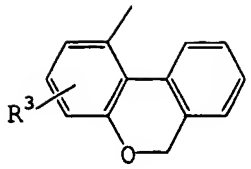


(wherein R^3 is a hydrogen atom, a hydroxyl group or a C_{1-10} alkoxy group); R^1 is a hydrogen atom, a C_{1-10} alkyl group, a C_{3-10} alkenyl group, a phenyl group, a pyrimidin-2-yl group or an amidyl group; and n is an integer of from 1 to 10], or a pharmaceutically acceptable salt thereof.

[Claim 4] The piperazine derivative of Formula [1] or a pharmaceutically acceptable salt thereof according to Claim 3 wherein Ar^2 is a substituted or unsubstituted naphthyl group.

[Claim 5] The piperazine derivative of Formula [1] or a pharmaceutically acceptable salt thereof according to Claim 3 wherein Ar^2 is a group represented by the formula:

[Formula 7]



(wherein R^3 is a hydrogen atom, a hydroxyl group or a C_{1-10} alkoxy group).

[Claim 6] A pharmaceutical preparation which comprises the piperazine derivative or a pharmaceutically acceptable salt thereof according to Claim 3.

[Claim 7] The pharmaceutical preparation according to Claim 6 which is a MC_4 receptor antagonist.

[Claim 8] The pharmaceutical preparation according to Claim 6 which is a therapeutic preparation for anxiety neurosis or depression.

[Detailed Description of the Invention]

[0001]

[Technical Field Pertinent to the Invention]

The present invention relates to a therapeutic preparation for anxiety neurosis or depression which comprises a MC_4 receptor antagonist as an effective ingredient, and relates to novel 1-(2-aryl-2-piperazinoethyl)piperazine derivatives having a MC_4 receptor antagonistic action.

[0002]

[Prior Art]

Mainstream drugs in the psychical field are drugs with which effect is clinically accepted by chance and development type drugs thereof. Recently, there are clinically used benzodiazepine (BZ) derivatives and 5-HT_{1A} acceptor agonists as anti-anxiety drugs, and SSRI, etc. as anti-depression drugs. Pharmacotherapy makes a developmental leap by the findings and creations of these drugs, however, these drugs are not created based on the cause of conditions and, as a result, relievable patients and unsuccessful conditions still remain.

[0003]

SRI is reported to be also effective on panic disorders and phobic disorders besides depression (Int. Clin. Psychopharmacol., 6, 5, 1992). Furthermore, there is an opinion that BZ derivatives are effective on depression, and they are actually prescribed in many cases in clinical. Actually, it is reported that 60 - 70 % of depression patients will be clinically accompanied by anxiety neurosis, and 40 - 90 % of anxiety neurosis patients will be clinically accompanied by depression (J. Clin. Psychiatry, 54, 75, 1993). As apparent from anxiety neurosis having been classified into panic disorder and generalized anxiety disorder according to the diagnostic standard of moral diseases (DSM-III), the concept and therapy of mental diseases recently have been changing a lot.

[0004]

As stated above, it is suggested that there is similarity in the occurrences of anxiety neurosis (DSM, panic disorder) and depression, and different approach from the previous concept is called for in drug development. It is also suggested by the recent progress of pathophysiology that stress is deeply pertinent to development mechanism of anxiety neurosis and depression. As an intracerebral reaction caused by stress, there has been known a functional abnormality of neuroendocrine system of which representative is the functional abnormality of hypothalamus-pituitary-adrenal system. From such a background, the neuropeptides which locate in pituitary and affect neuroendocrine attract attention as a development reason of depression/anxiety.

[0005]

Among such neuropeptides are corticotropin releasing factors (CRF) and POMC. CRF is known to play the central role of stress reaction such as susceptibility of hypothalamus-pituitary-adrenal system, and suggested to have relation to anxiety/depression. Melanocortins (ACTH, MSH) produced from POMC are main neuropeptides in hypothalamus, but there is no report of the substances acting to melanocortin receptors relating to stress reaction and depression/anxiety neurosis. Summary of the research on melanocortin receptors at this time is as follows.

Melanocortin receptors are classified into 5 subtypes of MC_1 - MC_5. For example, ACTH and α-MSH are reported to cause anxiogenic-like symptoms in the animal experiments (Pharmacol.Biochem. Behav., 36, 631, 1990; Peptides, 17, 171, 1996,; ibid, 11, 647, 1990; ibid, 11, 915, 1990; Pharmacol. Biochem. Behav., 12, 711, 1980). However, ACTH and α-MSH are subtype non-specific agonists, and the relation of melanocortin receptor subtypes and anxiety and depression has not been clarified. Furthermore, the relation of melanocortin receptor subtypes and stress reaction has not been clarified, either.

[0006]

MC_4 is reported as peptidergic selective agonist or antagonist. Compound 4 of the present invention in Table 1 acts as a high selective antagonist in recombinant human melanocortin receptors. In the past, there are not reported at all on stress reaction and anxiety reaction of these agonists and antagonists.

[0007]

[Problem to be solved by the Invention]

The relation of melanocortin receptor subtypes and anxiety/depression and stress reaction, and novel piperazine derivatives have been investigated.

[0008]

[Means for Solving Problem]

As a result of extensive research of the

above-mentioned subject, MC_4 receptor agonists have been found to have anxiety inducing action, and MC_4 receptor antagonists have been found to be effective for treatment of anxiety neurosis and depression because of their anti-stress, anti-anxiety and anti-depression actions. Furthermore, novel 1-(arryl-2-piperazinoethyl)piperazine derivatives of MC_4 receptor antagonists have been found, and thereby the present invention has been accomplished.

[0009]

The present invention is illustrated as follows:

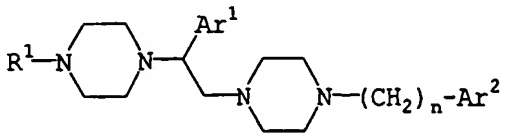
The present invention contains the below-mentioned items 1 - 6.

1. A therapeutic preparation for anxiety neurosis or depression which comprises a MC_4 receptor antagonist as an effective ingredient.

2. The therapeutic preparation for anxiety neurosis or depression wherein the MC_4 receptor antagonist is a piperazine derivative represented by Formula [1]:

[0010]

[Formula 8]



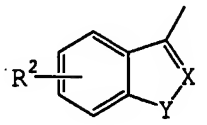
[1]

[0011]

[wherein Ar^1 is a substituted or unsubstituted phenyl group, or a substituted or unsubstituted naphthyl group; Ar^2 is a substituted or unsubstituted naphthyl group, a quinolyl group, a group represented by the formula:

[0012]

[Formula 9]

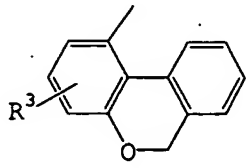


[0013]

(wherein R^2 is a hydrogen atom or a halogen atom; and X-Y is C-NH, C-O, C-S or N-O) or a group represented by the formula:

[0014]

[Formula 10]



[0015]

(wherein R^3 is a hydrogen atom, a hydroxyl group or a C_{1-10} alkoxy group); R^1 is a hydrogen atom, a C_{1-10} alkyl group, a C_{3-10} alkenyl group, a phenyl group, a pyrimidin-2-yl group or an amidyl group; and n is an integer of from 1 to 10], or a pharmaceutically

acceptable salt thereof.

3. The piperazine derivative or a pharmaceutically acceptable salt thereof represented by the above-mentioned Formula 1.

4. A pharmaceutical preparation which comprises as an effective ingredient the piperazine derivative or a pharmaceutically acceptable salt thereof of the above-mentioned Formula 1.

5. The above-mentioned pharmaceutical preparation which is a MC_4 receptor antagonist.

6. The above-mentioned pharmaceutical preparation which is a therapeutic preparation for anxiety neurosis or depression.

[0016]

In the present invention, the antagonist which belongs to MC_4 receptor means a compound which has an antagonistic action to MC_4 receptor, and preferably means a compound having an concentration-dependent inhibition action in the receptor binding test using MC_4 receptor-expressed cells according to the method described in J. Biol. Chem., 268; 15174-15179, 1993, having equivalent or higher affinity to MC_4 receptor than α-MSH, and antagonizing to an action of α-MSH when the amount of cAMP stimulated by α-MSH is measured by means of a cAMP measurement kit.

[0017]

In the present invention, the substituted

phenyl group refers to a phenyl group substituted with 1 to 3 substituents selected arbitrarily from the group consisting of a C_{1-10} alkyl group, a C_{1-10} alkoxy group, an aralkyloxy group, a hydroxyl group, a halogen atom, a nitro group, an amino group, an amino group substituted with one or two C_{1-6} alkyl groups, a trifluoromethyl group and a phenyl group; and examples of which are a 2-methylphenyl group, a 3-methylphenyl group, a 4-methylphenyl group, a 2-ethylphenyl group, a 3-ethylphenyl group, a 4-ethylphenyl group, a 2-propylphenyl group, a 3-propylphenyl group, a 4-propylphenyl group, a 2-cyclopentylphenyl group, a 2-methoxyphenyl group, a 3-methoxyphenyl group, a 4-methoxyphenyl group, a 4-ethoxyphenyl group, a 4-isopropoxyphenyl group, a 4-benzyloxyphenyl group, a 4-hydroxyphenyl group, a 2-fluorophenyl group, a 3-fluorophenyl group, a 4-fluorophenyl group, a 2-chlorophenyl group, a 3-chlorophenyl group, a 4-chlorophenyl group, a 2-bromophenyl group, a 3-bromophenyl group, a 4-bromophenyl group, a 4-nitrophenyl group, a 4-aminophenyl group, a 4-trifluoromethylphenyl group and a 4-biphenyl group.

[0018]

The substituted naphthyl group refers to a naphthyl group substituted with 1 to 3 substituents selected arbitrarily from the group consisting of a C_{1-10} alkyl group, a C_{1-10} alkoxy group, an aralkyloxy

group, a hydroxyl group, a halogen atom, a nitro group, an amino group, an amino group substituted with one or two C_{1-6} alkyl groups, a trifluoromethyl group and a phenyl group; and examples of which are a 2-methylnaphthalen-1-yl group, a 3-methylnaphthalen-1-yl group, a 4-methylnaphthalen-1-yl group, a 2-ethylnaphthalen-1-yl group, a 3-ethylnaphthalen-1-yl group, a 4-ethylnaphthalen-1-yl group, a 2-propylnaphthalen-1-yl group, a 3-propylnaphthalen-1-yl group, a 4-propylnaphthalen-1-yl group, a 2-methoxynaphthalen-1-yl group, a 3-methoxynaphthalen-1-yl group, a 4-methoxynaphthalen-1-yl group, a 6-methoxynaphthalen-1-yl group, a 4-ethoxynaphthalen-1-yl group, a 4-isopropoxynaphthalen-1-yl group, a 4-benzyloxynaphthalen-1-yl group, a 4-hydroxynaphthalen-1-yl group, a 2-fluoronaphthalen-1-yl group, a 3-fluoronaphthalen-1-yl group, a 4-fluoronaphthalen-1-yl group, a 2-chloronaphthalen-1-yl group, a 3-chloronaphthalen-1-yl group, a 4-chloronaphthalen-1-yl group, a 2-bromonaphthalen-1-yl group, a 3-bromonaphthalen-1-yl group, a 4-bromonaphthalen-1-yl group, a 4-nitronaphthalen-1-yl group, a 4-aminonaphthalen-1-yl group, a 4-trifluoromethylnaphthalen-1-yl group and a 4-dimethylaminonaphthalen-1-yl group.

[0019]

The C_{1-10} alkyl group refers to a straight,

branched or cyclic alkyl group, and examples which are a methyl group, an ethyl group, a propyl group, an isopropyl group, a cyclopropyl group, a butyl group, an isobutyl group, a cyclobutyl group, a cyclopropylmethyl group, a pentyl group, an isopentyl group, a cyclopentyl group, a cyclobutylmethyl group, a 1-ethylpropyl group, a hexyl group, an isohexyl group, a cyclohexyl group, a cyclopentylmethyl group, a 1-ethylbutyl group, a heptyl group, an isoheptyl group, a cyclohexylmethyl group, an octyl group, a nonyl group and a decyl group. The C_{3-10} alkenyl group refers to a straight, branched or cyclic alkenyl group; and examples of which are an allyl group, a 1-buten-4-yl group, a 2-buten-4-yl group, a 1-penten-5-yl group, a 2-penten-5-yl group and a prenyl group. The C_{1-10} alkoxy group refers to a straight, branced or cyclic alkoxy group; and examples of which are a methoxy group, an ethoxy group, a propoxy group, an isopropoxy group, a butoxy group, an isobutoxy group, a cyclopropylmethoxy group, a pentyloxy group, an isopentyloxy group, a hexyloxy group, a heptyloxy group, an octyloxy group, a nonyloxy group and a decyloxy group. The amino group substituted with one or two C_{1-6} alkyl groups refers to an amino group substituted with 1 or 2 members of a straight, branched or cyclic alkyl group; and examples of which are a methylamino group, an ethylamino group, a propylamino group, a dimethylamino group, diethylamino group and a dipropylamino group.

The halogen atom refers to a fluorine atom, a chlorine atom, a bromine atom or an iodine atom.

[0020]

Examples of the pharmaceutically acceptable salt in the present invention are salts with mineral acids such as sulfuric acid, hydrochloric acid or phosphoric acid, or salts with organic acids such as acetic acid, oxalic acid, lactic acid, tartaric acid, fumaric acid, maleic acid, methanesulfonic acid or benzenesulfonic acid.

[0021]

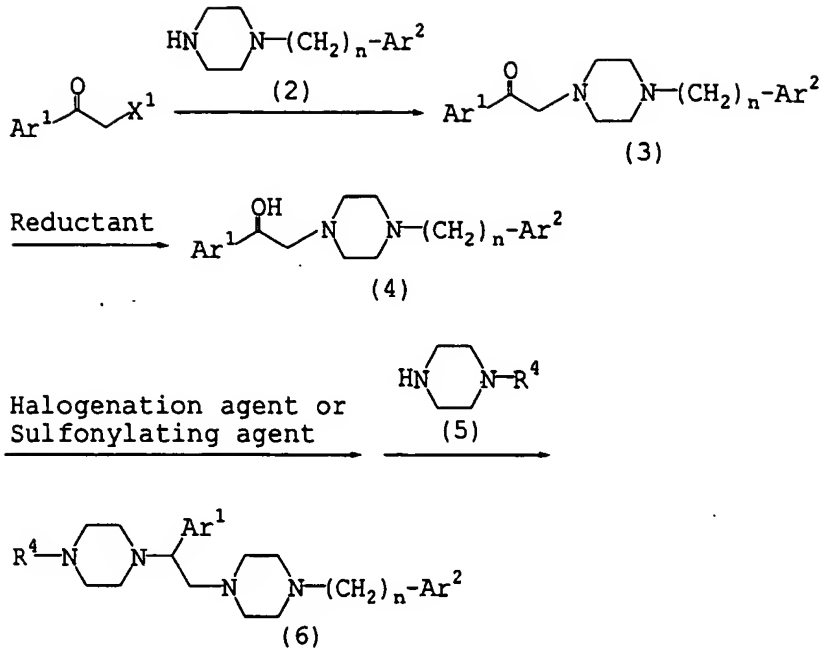
[Mode for Carrying Out the Invention]

The compounds of Formula [1] can be prepared by the following General Preparation Methods 1 to 4 (in the following reaction schemes, Ar^1, Ar^2 and R^1 are defined above; X^1 is a chlorine atom, a bromine atom or an iodine atom; R^4 is a C_{1-10} alkyl group, a C_{3-10} alkenyl group, a phenyl group or a pyrimidin-2-yl group; R^5 is an ordinary amino-protective group such as a t-butoxycarbonyl group, an ethoxycarbonyl group or a benzyloxycarbonyl group; R^6 is a C_{1-10} alkyl group; R^7 is a C_{1-10} alkyl group or an amidino group and Boc group is a t-butoxycarbonyl group).

[General preparation method 1]

[0022]

[Formula 11]



[0023]

A compound (1) can be reacted with a compound (2) in the presence or absence of a base in an inert solvent to convert to a compound (3), followed by reduction of the carbonyl group in an inert solvent to synthesize a compound (4). The compound (4) can be reacted with a halogenating agent or a sulfonylating agent such as an alkylsulfonyl halide or an arylsulfonyl halide in the presence or absence of a base in an inert solvent, thereby the hydroxyl group is converted to a suitable leaving group. Then, a piperazine derivative (5) can be reacted in the presence or absence of a base in an inert solvent to give a compound (6) of the present invention.

[0024]

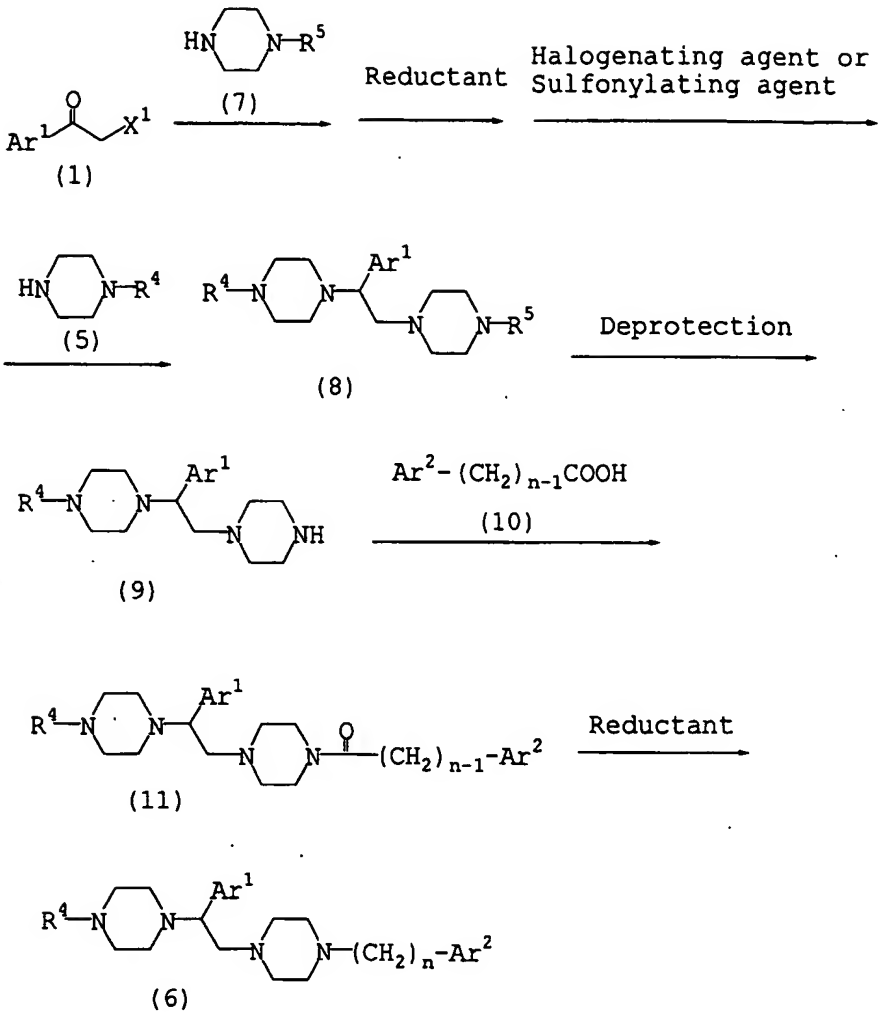
The base includes, for example, organic amines (e.g., triethylamine, diisopropylethylamine and pyridine) and inorganic bases (e.g., potassium carbonate, sodium bicarbonate, sodium hydroxide, potassium hydroxide and sodium hydride). The reduction includes, for example, a reduction under an acidic, neutral or basic condition using a boron reductant (e.g., sodium borohydride, sodium cyanoborohydride, lithium borohydride, L-Selectride and K-Selectride) or an aluminum reductant (e.g., lithium aluminum hydride, Red-Al or diisobutyl aluminum hydride). The halogenating agent includes, for example, an ordinary halogenating agent of the alcohol (e.g., thionyl chloride, thionyl bromide or phosphoryl chloride). The sulfonylating agent such as an alkylsulfonyl halide or an arylsulfonyl halide includes, for example, ordinary sulfonylating agents of the alcohol (e.g., methanesulfonyl chloride, benzenesulfonyl chloride, toluenesulfonyl chloride or trifluoromethanesulfonyl chloride). The inert solvent includes, for example, alcohols (e.g., methanol and ethanol), ethers (e.g., diethyl ether and tetrahydrofuran), hydrocarbons (e.g., toluene and benzene), halogenated carbon type solvents (e.g., chloroform and dichloromethane), dimethyl-formamide, acetonitrile, water and a mixture thereof.

[0025]

[General preparation method 2]

[0026]

[Formula 12]



[0027]

Following the procedure similar to that of (6) from (1) of the general preparation method 1, a compound (8) can be prepared from the compound (1). Then, the

amino group of the compound (8) can be deprotected to give a compound (9), which can be then condensed with a compound (10) in an inert solvent to give a compound (11). The amide group of the compound (11) can be reduced in an inert solvent to give the compound (6) of the present invention.

[0028]

The deprotection of the compound (8) can be carried out using the method described in Protective Groups in Organic Synthesis, by Theodora W. Greene and Peter G. M. Wuts. The condensation includes, for example, an amidation via an acid halide(e.g., an acid chloride and an acid bromide), an amidation via a mixed acid anhydride using ethyl chlorocarbonate, isobutyl chlorocarbonate, etc., and an amidation using a condensing agent such as 1-(3,3-dimethylaminopropyl)-3-ethylcarbodiimide, 1,3-dicyclohexylcarbodiimide, diphenylphosphoryl azide, diethyl cyanophosphate or carbonylimidazole. The reduction of the compound (11) includes, for example, a reduction under an acidic, neutral or basic condition using a boron reductant (e.g., diborane) or an aluminum reductant (e.g., lithium aluminum hydride, Red-Al and diisopropyl aluminum hydride). The inert solvent includes, for example, alcohols (e.g., methanol and ethanol), ethers (e.g., diethyl ether and tetrahydrofuran), hydrocarbons (e.g., toluene and benzene), halogenated carbon type solvents

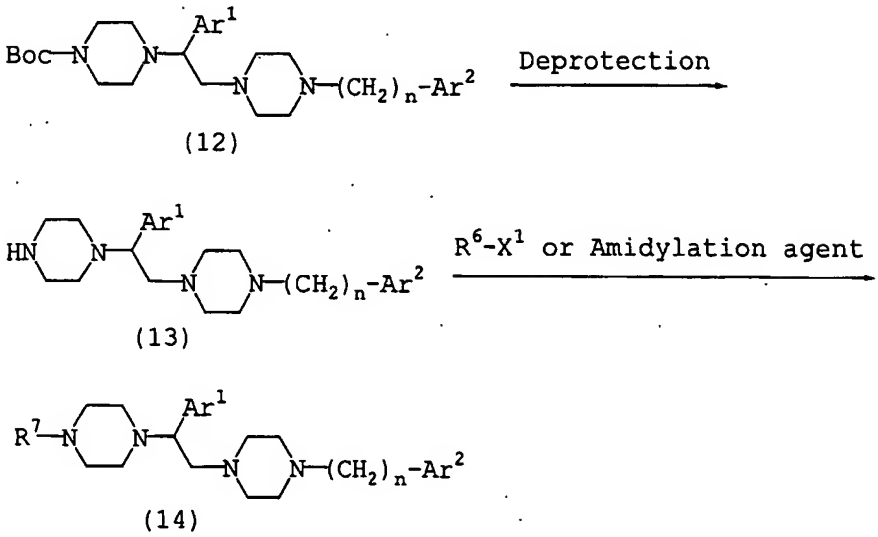
(e.g., chloroform and dichloromethane), dimethylformamide, acetonitrile, water and a mixture thereof.

[0029]

[General preparation method 3]

[0030]

[Formula 13]



[0031]

Following the procedure similar to that of (6) from (1) of the general preparation method 1, a compound (12) can be prepared from the compound (1). Removal of the Boc group of the compound (12) can give a compound (13) of the present invention. Then, the compound (13) can be reacted with an alkylating agent or an amidylating agent in the presence or absence of a base in an inert solvent to give a compound (14) of the

present invention.

[0032]

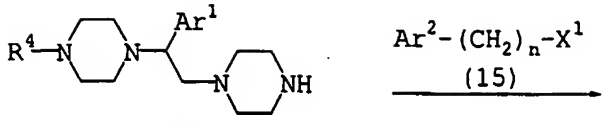
The removal of the Boc group of the compound (12) can be carried out according to the method described in Protective Groups in Organic Synthesis, by Theodora W. Greene and Peter G. M. Wuts. The alkylating agent includes, for example, alkyl halides (e.g., methyl iodide, ethyl iodide, 1-bromopropane and 2-bromopropane), alkyl sulfates (e.g., dimethyl sulfate and diethyl sulfate). The amidylating agent includes, for example, an amidylating agent such as cyanamide, S-methylthiourea and aminoiminomethanesulfonic acid. The base include, for example, organic amines (e.g., triethylamine, diisopropylethylamine and pyridine) and inorganic bases (e.g., potassium carbonate, sodium bicarbonate, sodium hydroxide, potassium hydroxide and sodium hydride). The inert solvent includes, for example, alcohols (e.g., methanol and ethanol), ethers (e.g., diethyl ether and tetrahydrofuran), hydrocarbons (e.g., toluene and benzene), halogenated carbon type solvents (e.g., chloroform and dichloromethane), dimethylformamide, acetonitrile, water and a mixture thereof.

[0033]

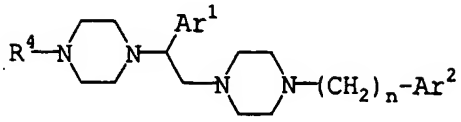
[General preparation method 4]

[0034]

[Formula 14]



(9)



(6)

[0035]

A compound (9) obtained according to the general preparation method 2 can be reacted with a compound (15) in the presence or absence of a base in an inert solvent to give the compound (6) of the present invention.

The base includes, for example, organic amines (e.g., triethylamine, diisopropylethylamine and pyridine) and inorganic bases (e.g., potassium carbonate, sodium bicarbonate, sodium hydroxide, potassium hydroxide and sodium hydride). The inert solvent includes, for example, alcohols (e.g., methanol and ethanol), ethers (e.g., diethyl ether and tetrahydrofuran), hydrocarbons (e.g., toluene and benzene), halogenated carbon type solvents (e.g., chloroform and dichloromethane), dimethylformamide, acetonitrile, water and a mixture thereof.

[0036]

[General preparation method 5]

Optically active compounds (6), (13) and (14) of the present invention can be obtained by optical resolution of racemic mixtures of the compounds (6), (13) and (14) of the present invention, respectively, by an ordinary optical resolution using an acidic chiral resolving agent or an optical resolution by HPLC using a chiral stationary phase. Further, an optically active compound (6) can be synthesized by resolving a racemic mixture of synthesis intermediate (4), (8), (9) or (11) by an optical resolution using an acidic chiral resolving agent or an optical resolution by HPLC using a chiral stationary phase and following the method described in the general preparation method 1 or 2. Furthermore, an optically active compound (13) or (14) can be synthesized by resolving a racemic mixture of synthesis intermediate (12) by an optical resolution using an acidic chiral resolving agent or an optical resolution by HPLC using a chiral stationary phase and following the method described in the general preparation method 3.

[0037]

The acidic chiral resolving agent includes, for example, optically active organic acids such as (+) or (-)-di-p-toluoyltartaric acid, (+) or (-)-dibenzoyltartaric acid, (+) or (-)-tartaric acid, (+) or (-)-mandelic acid, (+) or (-)-camphoric acid, or (+) or (-)-camphor-sulfonic acid.

The chiral stationary phase includes, for example, cellulose ester, cellulose carbamate, amylose carbamate, crown ether or polymethacrylate or derivatives thereof.

[0038]

The compounds of the present invention can be administered orally or parenterally, and the dosage forms thereof are, for example, tablets, capsules, granules, fine-powders, powders, troches, ointments, creams, emulsions, suspensions, suppositories and injections, all of which can be prepared by conventional preparation techniques (e.g., the methods defined in Japanese Pharmacopoeia, 12th edition). These dosage forms can be suitably chosen according to conditions and age of the patient and the purpose of therapy. These forms can be prepared by using conventional excipients (e.g., crystalline cellulose, starches, lactose and mannitol), binders (e.g., hydroxypropyllcellulose and polyvinylpyrrolidone), lubricants (e.g., magnesium stearate and talc), disintegrators (e.g., carboxymethylcellulose calcium).

The dose of the compound of the present invention for the treatment of adult human may range from 1 to 2000 mg per day, in a single portion or several divided portions, and can be suitably increased or decreased depending on age, body weight and conditions of the patient.

[0039]

[Embodiment]

The present invention is illustrated in more detail by the following examples and experiments.

[0040]

Example 1

Synthesis of 1-[2-(4-methoxyphenyl)-2-(4-methylpiperazino)ethyl]-4-(4-naphthalen-1-yl-butyl)piperazine trimaleate (Compound 32 in Table 1)

(1) In 6.0 ml of chloroform was dissolved 0.69 g of 4-methoxyphenacyl bromide, and 3.0 ml of N-ethyldiisopropylamine and 1.20 g of 1-(4-naphthalen-1-yl-butyl)piperazine dihydrochloride were added, followed by reflux with heating for an hour. The reaction solution was concentrated under reduced pressure. To the residue was added a saturated aqueous sodium bicarbonate solution and, after extraction with ethyl acetate, the organic layer was dried over anhydrous sodium sulfate. After removal of the drying agent by filtration, the filtrate was concentrated under reduced pressure to give a crude 1-[2-(4-methoxyphenyl)-2-oxoethyl]-4-(4-naphthalen-1-yl-butyl)piperazine.

[0041]

(2) The crude 1-[2-(4-methoxyphenyl)-2-oxoethyl]-4-(4-naphthalen-1-yl-butyl)piperazine obtained in (1) was dissolved in 10 ml of ethanol, and then a solution prepared by adding 1 drop of 10 % aqueous

potassium hydroxide solution and 0.18 g of sodium borohydride to 1.0 ml of water was added, followed by stirring at 50°C for an hour. To the reaction solution was poured water and, after extraction with ethyl acetate, the organic layer was dried over anhydrous sodium sulfate. After removal of the drying agent by filtration, the filtrate was concentrated under reduced pressure to give a crude 1-[2-hydroxy-2-(4-methoxyphenyl)ethyl]-4-(4-naphthalen-1-yl-butyl)piperazine.

[0042]

(3) The crude 1-[2-hydroxy-2-(4-methoxyphenyl)ethyl]-4-(4-naphthalen-1-yl-butyl)piperazine obtained in (2) and 1.25 ml of triethylamine were dissolved in 10 ml of methylene chloride and, after ice-cooling, 0.46 ml of methanesulfonyl chloride was added, followed by stirring at room temperature for 30 minutes. To the reaction solution were added 0.84 ml of triethylamine and 1.0 ml of 1-methylpiperazine, successively, followed by stirring at room temperature for 3 hours. After concentration of the reaction solution under reduced pressure, a saturated aqueous sodium bicarbonate solution was poured and, after extraction with ethyl acetate, the organic layer was dried over anhydrous sodium sulfate. After removal of the drying agent by filtration, the filtrate was concentrated under reduced

pressure, and the residue was purified by a silica gel column chromatography (Chromatorex NH, hexane : ethyl acetate =1:1) to give 0.94 g of 1-[2-(4-methoxyphenyl)-2-(4-methylpiperazino)ethyl]-4-(4-naphthalen-1-yl-butyl)piperazine.

[0043]

(4) 0.94 g of 1-[2-(4-Methoxyphenyl)-2-(4-methylpiperazino)ethyl]-4-(4-naphthalen-1-yl-butyl)piperazine was dissolved in 5.0 ml of ethanol, 5.0 ml of an ethanol solution of 0.56 g of maleic acid was added, followed by being allowed to stand for 2 hours. The precipitated crystals were collected by filtration and washed with ethanol to give 1.24 g of 1-[2-(4-methoxyphenyl)-2-(4-methylpiperazino)ethyl]-4-(4-naphthalen-1-yl-butyl)piperazine trimaleate as crystals.

The structures and physical property data of the present compound and the compounds prepared similarly are shown in Table 1.

[0044]

Example 2

Synthesis of 1-[2-(4-fluorophenyl)-2-(4-methylpiperazino)ethyl]-4-(4-naphthalen-1-yl-butyl)piperazine tetrahydrochloride (Compound 4 in Table 1)

(1) 4.3 g of 2-Chloro-4'-fluoroacetophenone and 8.0 g of 1-ethoxycarbonylpiperazine were dissolved in 30 ml of chloroform and refluxed with heating for 2

hours. After cooling to room temperature, the reaction solution was concentrated under reduced pressure, and a conc. aqueous ammonia solution was added, followed by extraction with ether. The organic layer was dried over anhydrous sodium sulfate. After removal of the drying agent by filtration, the filtrate was concentrated under reduced pressure to give a crude 1-ethoxycarbonyl-4-[2-(4-fluorophenyl)-2-oxoethyl]piperazine, which was then dissolved in 40 ml of ethanol, and an aqueous solution dissolved 1 drop of 5 % potassium hydroxide and 1.0 g of sodium borohydride in 5 ml of water was added, followed by heating at 50°C for an hour. After concentration of the reaction solution under reduced pressure, water was added, followed by extraction with ether, and the organic layer was dried over anhydrous sodium sulfate. After removal of the drying agent by filtration, the filtrate was concentrated under reduced pressure. To the residue was poured 50 ml of 4M hydrogen chloride/ethyl acetate solution, the solution was concentrated under reduced pressure, and the resulting solid was washed with ether to give 8.3 g of 1-ethoxycarbonyl-4-[2-(4-fluorophenyl)-2-hydroxyethyl]piperazine hydrochloride.

[0045]

(2) To 8.3 g of 1-ethoxycarbonyl-4-[2-(4-fluorophenyl)-2-hydroxyethyl]piperazine hydrochloride were added 20 ml of benzene and 2.5 ml of thionyl

chloride, followed by heating at 50°C for 10 minutes. The reaction solution was concentrated under reduced pressure, a saturated aqueous ammonia solution and water were poured, followed by extraction with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and, after removal of the drying agent by filtration, the filtrate was concentrated under reduced pressure. To the residue was poured 4M hydrogen chloride/ethyl acetate solution, the solution was concentrated under reduced pressure, and the resulting solid was washed with ether to give 8.1 g of 1-ethoxycarbonyl-4-[2-chloro-2-(4-fluorophenyl)ethyl]-piperazine hydrochloride.

[0046]

(3) To 7.6 g of 1-ethoxycarbonyl-4-[2-chloro-2-(4-fluorophenyl)ethyl]piperazine hydrochloride were poured 5 ml of a saturated aqueous ammonia solution and water and, after extraction with ether, the organic layer was dried over anhydrous sodium sulfate. After removal of the drying agent by filtration, the filtrate was concentrated under reduced pressure. The residue was dissolved in 20 ml of benzene, and 5.4 ml of 1-methylpiperazine was added, followed by heating at 65°C for 3.5 hours. To the reaction solution were poured a saturated aqueous ammonia solution and water and, after extraction with ether, the organic layer was dried over anhydrous sodium sulfate. After removal of the drying

agent by filtration, the filtrate was concentrated under reduced pressure. The residue was purified by a silica gel column chromatography (Chromatorex NH, hexane : ethyl acetate =4:1) to give 6.58 g of 1-ethoxycarbonyl-4-[2-(4-fluorophenyl)-2-(4-methylpiperazino)ethyl]piperazine as an oil.

[0047]

(4) 1.25 g of 1-Ethoxycarbonyl-4-[2-(4-fluorophenyl)-2-(4-methylpiperazino)ethyl]piperazine was dissolved in 2 ml of ethanol, and 1.3 g of potassium hydroxide was added, followed by reflux with heating for an hour. The reaction solution was cooled to room temperature and, after addition of 2 ml of water, extracted with ethyl acetate, and the organic layer was dried over anhydrous sodium sulfate. After removal of the drying agent by filtration, the filtrate was concentrated under reduced pressure to give 1.0 g of a crude 1-[2-(4-fluorophenyl)-2-(4-methyl-piperazino)ethyl]piperazine.

[0048]

(5) 0.37 g of 4-Naphthalen-1-yl-butyric acid was dissolved in 5.0 ml of toluene, and 0.35 ml of thionyl chloride and 1 drop of dimethylformamide were added, followed by heating at 70°C for 30 minutes. The reaction solution was concentrated under reduced pressure to give a crude 4-naphthalen-1-yl-butyryl chloride. To the resulting crude 4-naphthalen-1-yl-

butyryl chloride was added 2.3 ml of a toluene solution of 0.40 mg of 1-[2-(4-fluorophenyl)-2-(4-methylpiperazino)ethyl]piperazine, followed by stirring at room temperature for 30 minutes. To the reaction solution was added a saturated aqueous sodium bicarbonate solution and, after extraction with ethyl acetate, the organic layer was dried over anhydrous sodium sulfate. After removal of the drying agent by filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by a silica gel column chromatography (Wako-gel C-200, chloroform : methanol =10:1) to give 0.58 g of 1-[2-(4-fluorophenyl)-2-(4-methylpiperazino)ethyl]-4-(4-naphthalen-1-yl-butyryl)piperazine as an oil.

[0049]

(6) 0.32 g of 1-[2-(4-Fluorophenyl)-2-(4-methylpiperazino)ethyl]-4-(4-naphthalen-1-yl-butyryl)piperazine was dissolved in 10 ml of tetrahydrofuran, and 50 mg of lithium aluminum hydride was added, followed by reflux with heating for 30 minutes. The reaction solution was cooled to room temperature and, after addition of 1 ml of 10 % aqueous sodium hydroxide solution, ether was poured, followed by drying over anhydrous sodium sulfate. After removal of the drying agent by filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by a silica gel column chromatography

(Chromatorex NH, hexane : ethyl acetate =1:1) to give 0.30 g of 1-[2-(4-fluorophenyl)-2-(4-methylpiperazino)ethyl]-4-(4-naphthalen-1-yl-butyl)piperazine as an oil.

[0050]

(7) 0.30 g of 1-[2-(4-Fluorophenyl)-2-(4-methylpiperazino)ethyl]-4-(4-naphthalen-1-yl-butyl)piperazine was dissolved in 4 ml of methanol, and 1 ml of 4M hydrogen chloride/ethyl acetate was added. The solution was concentrated under reduced pressure, and the resulting solid was washed with methanol to give 0.20 g of 1-[2-(4-fluorophenyl)-2-(4-methylpiperazino)ethyl]-4-(4-naphthalen-1-yl-butyl)piperazine tetrahydrochloride.

The structures and physical property data of the present compound and the compounds prepared similarly are shown in Table 1.

[0051]

Example 3

Synthesis of 1-[2-(4-fluorophenyl)-2-(4-isopropylpiperazino)ethyl]-4-(4-naphthalen-1-yl-butyl)piperazine trimaleate (Compound 16 in Table 1)

(1) 0.62 g of 1-[2-(4-Fluorophenyl)-2-(4-t-butoxycarbonylpiperazino)ethyl]-4-(4-naphthalen-1-yl-butyl)piperazine was dissolved in a mixture of 3 ml of ethyl acetate and 3 ml of methanol, and 4 ml of 4M hydrogen chloride/ethyl acetate was added, followed by

stirring at room temperature for 6 hours. The precipitated crystals were collected by filtration, and the crystals were washed with ethyl acetate to give 0.42 g of 1-[2-(4-fluorophenyl)-2-piperazinoethyl]-4-(4-naphthalen-1-yl-butyl)piperazine tetrahydrochloride.

[0052]

(2) 0.2 g of 1-[2-(4-Fluorophenyl)-2-piperazinoethyl]-4-(4-naphthalen-1-yl-butyl)piperazine tetrahydrochloride was dissolved in 0.7 ml of dimethylformamide, and 74 mg of 60 % sodium hydride in oil was added with ice-cooling. The temperature was elevated to room temperature, followed by stirring for 10 minutes. To the reaction solution was added a 0.3 ml of dimethylformamide solution of 0.2 g of 2-bromopropane, followed by stirring overnight. The reaction solution was poured to water and, after extraction with ethyl acetate, the organic layer was washed with a saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate. After removal of the drying agent by filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by a silica gel column chromatography (Chromatorex NH, hexane : ethyl acetate =1:1) to give 0.13 g of 1-[2-(4-fluorophenyl)-2-(4-isopropylpiperazino)ethyl]-4-(4-naphthalen-1-yl-butyl)piperazine as an oil.

[0053]

(3) 0.13 g of 1-[2-(4-Fluorophenyl)-2-(4-isopropylpiperazino)ethyl]-4-(4-naphthalen-1-yl-butyl)piperazine was dissolved in 1.5 ml of ethanol, and 1 ml of an ethanol solution of 0.11 g of maleic acid was added, followed by allowing to stand for 2 hours. The precipitated crystals were collected by filtration and washed with ethanol to give 0.18 g of 1-[2-(4-fluorophenyl)-2-(4-isopropylpiperazino)ethyl]-4-(4-naphthalen-1-yl-butyl)piperazine trimaleate as crystals.

The structures and physical property data of the present compound and the compounds prepared similarly are shown in Table 1.

[0054]

Example 4

Synthesis 4-{1-(4-fluorophenyl)-2-[4-(4-naphthalen-1-yl-butyl)piperazin-1-yl]ethyl}piperazine-1-carboxamidine (Compound 20 in Table 1)

0.72 g of 1-[2-(4-Fluorophenyl)-2-piperazinoethyl]-4-(4-naphthalen-1-yl-butyl)piperazine tetrahydrochloride obtained in Example 3(1) was dissolved in 10 ml of ethanol, and 0.20 g of cyanamide was added, followed by reflux with stirring for 4 hours. After cooling to room temperature, the reaction solution was concentrated under reduced pressure, a saturated aqueous sodium bicarbonate solution was added and, after extraction with ethyl acetate, the organic layer was dried over anhydrous sodium sulfate. After removal of

the drying agent by filtration, the filtrate was concentrated under reduced pressure. The residue was dissolved in 3.0 ml of ethanol, and 3.0 ml of an ethanol solution of 0.50 g of maleic acid was added, followed by allowing to stand for 2 hours. The precipitated crystals were collected by filtration and washed with ethanol to give 0.52 g of 4-{1-(4-fluorophenyl)-2-[4-(4-naphthalen-1-yl-butyl)piperazin-1-yl]ethyl}piperazine-1-carboxamidine trimaleate as crystals.

The structures and physical property data of the present compound and the compounds prepared similarly are shown in Table 1.

[0055]

Example 5

Synthesis of 1-[2-(4-aminophenyl)-2-(4-methylpiperazino)ethyl]-4-(4-naphthalen-1-yl-butyl)piperazine trimaleate (Compound 39 in Table 1)

0.54 g of 1-[2-(4-Nitrophenyl)-2-(4-methylpiperazino)ethyl]-4-(4-naphthalen-1-yl-butyl)piperazine trimaleate obtained by the procedure similar to that of Example 1 was dissolved in 1M aqueous sodium hydroxide solution and extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate. After removal of the drying agent by filtration, the filtrate was concentrated under reduced pressure. The residue was dissolved in 20 ml of ethanol, and 10 mg of platinum oxide was added, followed

by stirring under a hydrogen atmosphere at room temperature for 2 hours. After removal of the platinum oxide by filtration, the filtrate was concentrated under reduced pressure. The residue was dissolved in 3.0 ml of ethanol, and 3.0 ml of an ethanol solution of 0.19 g of maleic acid was added, followed by allowing to stand for 2 hours. The precipitated crystals were collected by filtration and washed with ethanol to give 0.35 g of 1-[2-(4-aminophenyl)-2-(4-methylpiperazino)ethyl]-4-(4-naphthalen-1-yl-butyl)piperazine trimaleate as crystals.

The structures and physical property data of the present compound and the compounds prepared similarly are shown in Table 1.

[0056]

Example 6

Synthesis of 1-[2-(4-fluorophenyl)-2-(4-methylpiperazino)ethyl]-4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)butyl]piperazine trimaleate (Compound 46 in Table 1)

(1) 0.37 g of 1-[2-(4-Fluorophenyl)-2-(4-methylpiperazino)ethyl]piperazine obtained in Example 2 (4) was dissolved in 4.0 ml of dimethylformamide, and 0.19 g of N-ethyldiisopropylamine and 0.31 g of 4-(6-fluoro-1,2-benzisoxazol-3-yl)butyl chloride were added, followed by stirring at 120°C for 3 hours. The reaction solution was cooled to room temperature, diluted with ethyl acetate and washed with water and a saturated

aqueous sodium chloride solution. The organic layer was dried over anhydrous sodium sulfate. After removal of the drying agent by filtration, the filtrate was concentrated under reduced pressure. The residue was purified by a silica gel column chromatography (Chromatorex NH, hexane : ethyl acetate =1:1) to give 0.22 g of 1-[2-(4-fluorophenyl)-2-(4-methylpiperazino)ethyl]-4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)butyl]piperazine as an oil.

[0057]

(2) 0.21 g of 1-[2-(4-Fluorophenyl)-2-(4-methylpiperazino)ethyl]-4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)butyl]piperazine was dissolved in 2.0 ml of ethanol, and 2.0 ml of an ethanol solution of 0.16 g of maleic acid was added, followed by allowing to stand for 2 hours. The precipitated crystals were collected by filtration and washed with ethanol to give 0.30 g of 1-[2-(4-fluorophenyl)-2-(4-methylpiperazino)ethyl]-4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)butyl]piperazine trimaleate as crystals.

The structures and physical property data of the present compound and the compounds prepared similarly are shown in Table 1.

[0058]

Example 7

Synthesis of 1-{2-(4-fluorophenyl)-2-[4-(2-propyl)piperazino]ethyl}-4-[4-(2-hydroxynaphthalen-1-

yl)butyl]piperazine trimaleate (Compound 55 in Table 1)

0.06 g of 1-{2-(4-Fluorophenyl)-2-[4-(2-propyl)piperazino]ethyl}-4-[4-(2-methoxynaphthalen-1-yl)butyl]piperazine obtained by the procedure similar to that of Example 2 was dissolved in 10 ml of 48 % aqueous hydrobromic acid solution and refluxed with heating for 2 hours. The reaction solution was cooled to room temperature and concentrated under reduced pressure, and 1M aqueous sodium hydroxide solution was added, followed by extraction with ether. The organic layer was dried over anhydrous sodium sulfate. After removal of the drying agent by filtration, the filtrate was concentrated under reduced pressure. Then, the residue was dissolved in 2.0 ml of ethanol and, after addition of 2.0 ml of an ethanol solution of 0.01 g of maleic acid, allowed to stand for 2 hours. The precipitated crystals were collected by filtration and washed with ethanol to give 0.06 g of 1-{2-(4-fluorophenyl)-2-[4-(2-propyl)piperazino]ethyl}-4-[4-(2-hydroxynaphthalen-1-yl)butyl]piperazine trimaleate as crystals.

The structures and physical property data of the present compound and the compounds prepared similarly are shown in Table 1.

[0059]

Example 8

Synthesis of 1-{2-(4-fluorophenyl)-2-[4-(2-propyl)piperazino]ethyl}-4-[4-(2-propoxynaphthalen-1-

yl)butyl]piperazine trimaleate (Compound 56 in Table 1)

(1) 0.05 g of 1-{2-(4-Fluorophenyl)-2-[4-(2-propyl)piperazino]ethyl}-4-[4-(2-hydroxynaphthalen-1-yl)butyl]piperazine trimaleate obtained in Example 7 was dissolved in 1M aqueous sodium hydroxide solution and extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate. After removal of the drying agent by filtration, the filtrate was concentrated under reduced pressure. Then, the residue was dissolved in 5 ml of dimethylformamide, and 0.19 g of potassium carbonate and 0.068 ml of 2-iodopropane were added, followed by stirring at 70°C for 6 hours. The reaction solution was cooled to room temperature, diluted with ethyl acetate, and washed with water and a saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous sodium sulfate. After removal of the drying agent by filtration, the filtrate was concentrated under reduced pressure. The residue was purified by a silica gel column chromatography (Chromatorex NH, hexane : ethyl acetate =1:1) to give 0.03 g of 1-{2-(4-fluorophenyl)-2-[4-(2-propyl)piperazino]ethyl}-4-[4-(2-propoxynaphthalen-1-yl)butyl]piperazine as an oil.

[0060]

(2) 0.03 g of 1-{2-(4-fluorophenyl)-2-[4-(2-propyl)piperazino]ethyl}-4-[4-(2-propoxynaphthalen-1-yl)butyl]piperazine was dissolved in 2.0 ml of ethanol,

and 2.0 ml of an ethanol solution of 0.02 g of maleic acid was added, followed by allowing to stand for 2 hours. The precipitated crystals were collected by filtration and washed with ethanol to give 0.03 g of 1-{2-(4-fluorophenyl)-2-[4-(2-propyl)piperazino]ethyl}-4-[4-(2-propoxynaphthalen-1-yl)butyl]piperazine trimaleate as crystals.

The structures and physical property data of the present compound and the compounds prepared similarly are shown in Tables 1.

[0061]

Example 9

Synthesis of 1-[2-(4-fluorophenyl)-2-(4-methylpiperazino)ethyl]-4-(4-naphthalen-1-yl-butyl)piperazine hydrochloride (Optically active compound)

1-[2-(4-Fluorophenyl)-2-(4-methylpiperazino)ethyl]-4-(4-naphthalen-1-yl-butyl)piperazine obtained in Example 2 (6) was resolved by means of HPLC (Chiralpak AD (manufactured by Daicel Co.), 2ϕx25cm, mobile phase: hexane-isopropanol-diethylamine=95:5:0.1, flow rate 5.0 ml/min). After the resolution, the solvent was concentrated under reduced pressure, dissolved in ethanol, and introduced to the hydrochloride by 4M hydrogen chloride/ethyl acetate, and the solvent was concentrated under reduced pressure to give 1-[2-(4-fluorophenyl)-2-(4-methylpiperazino)ethyl]-

4-(4-naphthalen-1-yl-butyl)piperazine hydrochloride (optically active compound).

[0062]

(+)-1-[2-(4-Fluorophenyl)-2-(4-methylpiperazino)ethyl]-4-(4-naphthalen-1-yl-butyl)piperazine hydrochloride

$[\alpha]_D^{25}$=+15.8(c=0.24, MeOH), Retention time; 7.0 minutes. m.p.193 - 195°C (ethanol)

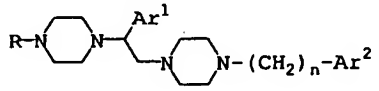
(-)-1-[2-(4-Fluorophenyl)-2-(4-methylpiperazino)ethyl]-4-(4-naphthalen-1-yl-butyl)piperazine hydrochloride

$[\alpha]_D^{25}$=-15.0(c=0.24, MeOH), Retention time; 10.9 minutes. m.p.193 - 195°C (ethanol)

The structures and physical property data of the present compound and the compounds prepared similarly are shown in Table 1.

[0063]

Table 1[*1]



Compound No.	Example No.	Ar^1	Ar^2	R^1	n	M.P.[*2] (°C)	Solvent for recrystalization
1	2	4-F-Ph	1-Naph	Me	1	173-175	Ether
2	2	4-F-Ph	1-Naph	Me	2	174-176	EtOH
3	2	4-F-Ph	1-Naph	Me	3	175-177	EtOH
4	2	4-F-Ph	1-Naph	Me	4	193-195[*3]	AcOEt
5[*10]	15	4-F-Ph	1-Naph	Me	4	193-195[*3]	EtOH
6[*11]	15	4-F-Ph	1-Naph	Me	4	193-195[*3]	EtOH
7	2	4-F-Ph	1-Naph	Me	5	170-172	EtOH
8	2	4-F-Ph	1-Naph	Me	6	182-184	EtOH
9	2	4-F-Ph	2-Naph	Me	1	189-191	EtOH-Ether
10	2	4-F-Ph	2-Naph	Me	2	187-189	EtOH
11	2	4-F-Ph	2-Naph	Me	3	180-182	EtOH
12	2	4-F-Ph	2-Naph	Me	4	185-187	EtOH
13	1	4-F-Ph	1-Naph	H	4	180-182[*3]	MeOH
14	3	4-F-Ph	1-Naph	Et	4	120-122	EtOH
15	3	4-F-Ph	1-Naph	Pr	4	150-152	EtOH
16	3	4-F-Ph	1-Naph	iPr	4	127-129	EtOH
17	1	4-F-Ph	1-Naph	cPr	4	161-163	EtOH
18	1	4-F-Ph	1-Naph	cHex	4	171-173	EtOH
19	1	4-F-Ph	1-Naph	Ph	4	172-174	EtOH-Ether
20	4	4-F-Ph	1-Naph	Amidyl	4	171-173	EtOH
21	1	4-F-Ph	1-Naph	Pyrimidin-2-yl	4	190-192	EtOH-Ether
22	2	1-Naph	1-Naph	Me	4	171-173	EtOH

Table 1-Continued

23	2	1-Naph	2-Naph	Me	4	80-83	EtOH
24	2	2-Naph	1-Naph	Me	4	122-124	EtOH
25	2	2-Naph	2-Naph	Me	4	133-135	EtOH
26	1	Ph	1-Naph	Me	4	167-169	EtOH
27	1	3-F-Ph	1-Naph	Me	4	173-175	EtOH
28	1	4-Cl-Ph	1-Naph	Me	4	175-177	EtOH
29	1	4-Me-Ph	1-Naph	Me	4	186-188	EtOH
30	1	2-MeO-Ph	1-Naph	Me	4	114-116	EtOH
31	1	3-MeO-Ph	1-Naph	Me	4	123-125	EtOH
32	1	4-MeO-Ph	1-Naph	Me	4	138-140	EtOH
33	1	2-Br-Ph	1-Naph	Me	4	amorphous[*4]	
34	1	3-Br-Ph	1-Naph	Me	4	119-121	EtOH
35	1	4-Br-Ph	1-Naph	Me	4	168-170	EtOH
36	1	4-Biphenyl	1-Naph	Me	4	123-125	EtOH
37	1	4-CF_3-Ph	1-Naph	Me	4	128-130	EtOH
38	1	4-NO_2-Ph	1-Naph	Me	4	176-178	EtOH
39	5	4-NH_2-Ph	1-Naph	Me	4	152-154	EtOH
40	1	4-BnO-Ph	1-Naph	Me	4	151-153	EtOH
41	2	4-F-Ph	4-Quinolyl	Me	4	159-161	EtOH
42	2	4-F-Ph	4-Me_2N-1-Naph	Me	4	173-175	EtOH
43	2	4-F-Ph	Benzo[b]furan-3-yl	Me	4	174-176	EtOH
44	2	4-F-Ph	Indole-3-yl	Me	4	163-165	EtOH
45	2	4-F-Ph	5-Cl-Benzothiophen-3-yl	Me	4	174-176	EtOH
46	6	4-F-Ph	6-F-1,2-Benzisoxazole-3-yl	Me	4	170-173	EtOH
47	2	4-F-Ph	4-Methoxy-6H-dibenzo[b,d]pyran-1-yl	iPr	3	93-95	EtOH
48	2	4-F-Ph	4-Methoxy-6H-dibenzo[b,d]pyran-1-yl	iPr	4	103-105	EtOH
49	1	4-F-Ph	4-Me_2N-1-Naph	iPr	4	122-124	EtOH
50	2	4-F-Ph	4-MeO-1-Naph	Me	4	178-181	EtOH
51	2	4-F-Ph	2-MeO-1-Naph	Me	4	173-175	EtOH
52	2	4-F-Ph	4-Me-1-Naph	Me	4	180-182	EtOH

Table 1-Continued

53	2	4-F-Ph	4-F-1-Naph	Me	4	174-176	EtOH
54	2	4-F-Ph	2-MeO-1-Naph	iPr	4	154-156	EtOH
55	7	4-F-Ph	2-OH-1-Naph	iPr	4	amorphous*5	
56	8	4-F-Ph	2-iPrO-1-Naph	iPr	4	167-169	EtOH

*1: Notation in Table 1
Ph=Phenyl, Naph=Naphtyl, Me=Methyl, Et=Ethyl, Pr=Propyl, Hex=Hexyl, Bn=Benzyl, iPr=Isopropyl, cPr=Cycropropyl, cHex=Cycrohexyl.

*2: Maleate unless otherwise noted

*3: Hydrochloride

*4: Compound ^{1}H-NMR (200MHz, $CDCl_3$) 1.6-1.8 (m,4H) 2.24 (s, 3H) 2.3-2.9 (m, 20H) 3.08 (t, 2H, J=7.5Hz) 4.12 (t, 1H, J=6.0Hz) 7.08 (m, 1H) 7.3-7.6 (m, 7H) 7.70 (m, 1H) 7.84 (m, 1H) 8.04 (m, 1H)
MS (m/z) 549 (M+H) 551 (M+2+H)

*5: Compound ^{1}H-NMR (300MHz, $CDCl_3$) 1.00 (d, 6H, J=7.5Hz) 1.60 (m, 2H) 1.72 (m, 2H) 2.4-2.8 (m, 20H) 2.94 (m, 3H) 3.56 (t, 1H, J=7.0Hz) 6.99 (m, 2H) 7.1-7.3 (m, 4H) 7.42 (m, 1H) 7.60 (d, 1H, J=8.0Hz) 7.75 (d, 1H, J=7.5Hz) 7.86 (d, 1H, J=7.5Hz).

*6: Optically active Compound 4 $[\alpha]_D^{25}$+15.8 (MeOH, c 0.24)

*7: Optically active Compound 4 $[\alpha]_D^{25}$-15.0 (MeOH, c 0.24)

[0066]

Experiment 1 [MC_4 receptor Binding Assay]

MC_4 receptor binding assay was carried out according to the method described in Pharmacology & Toxicology, 79, 161-165, 1996. HEK-293 cell membranes expressing the human MC_4 receptor were purchased from Biolinks Co. The cell membranes were homogenized in a 50 mM Tris hydrochloric acid buffer solution (pH 7.4) containing 2 mM ethylenediamine tetraacetic acid, 10 mM calcium chloride and 100 μM phenylmethanesulfonyl-fluoride. The homogenate was centrifuged at 48,000 x g for 20 minutes at 4°C. The precipitate obtained by centrifugation was again homogenized in the same buffer solution, and the homogenate was centrifuged at 48,000 x g for 20 minutes at 4°C. This procedure was repeated twice. The precipitate was suspended in 50 mM Tris hydrochloric acid buffer solution (pH 7.4) containing 2 mM ethylenediamine tetraacetic acid, 10 mM calcium chloride, 100 μM phenylmethanesulfonylfluoride and 0.1 % bovine serum albumin to adjust to a protein concentration of 100 μg/ml to give a crude membrane preparation which was used for the binding assay. The crude membrane preparation (0.25 ml, 25 μg protein) was reacted with [^{125}I]Nle^4-D-Phe^7-α-MSH (final concentration; 0.2 nM) at 25°C for 120 minutes. After the completion of the reaction, the reaction solution was filtered under suction on GF/C glass filter

presoaked for 2 hours in 50 mM Tris hydrochloric acid buffer solution (pH 7.4) containing 0.5 % bovine serum with the use of a cell harvester for receptor binding assay. The radioactivity on the filter paper was measured in a gamma-counter. The binding in the presence of 1 μM Nle^4-D-Phe^7-α-MSH was defined as non-specific binding. Specific binding was obtained by subtracting the non-specific binding from the total binding, which was the binding in the absence of 1 μM Nle^4-D-Phe^7-α-MSH. Test drug was dissolved in 100 % DMSO, and added simultaneously with [^{125}I]Nle^4-D-Phe^7-α-MSH to the membrane preparation. The IC_{50} value was calculated from the inhibition curve in the concentration of 10^{-9} - 10^{-5}. As a result, for example, Compound 4 shows 164 nM, and optically active Compound 6 shows 90 nM.

[0067]

Experiment 2

Anxiogenic-like activity inducing action by α-MSH and MTII in Vogel test in rat (Proconflict test) was studied.

α-MSH and MTII were purchased from Peninsula Laboratories. Male SD rats weighing 220 to 240 g (Charles River Japan Inc.) were used for animals. Rats deprived of drinking water for 48 hours were divided into 5 animals for each group. The test drug was administered to rats intracerbroventricularly at 10 μl/2

min. of the test compound which was prepared by dissolving a predetermined amount of α-MSH or MTII in saline containing 0.1 % bovine serum albumin. To control rats which were not administered test compound, saline containing 0.1% bovine serum albumin was administered intracerebroventricularly at 10 µl/2 min. Thirty minutes after the administration, rats were placed in a apparatus for the test, and drinking behaviors during the time of free access to drinking water for 3 minutes were measured. During the time of free access to drinking water, an electric shock (0.4 mA) was released, every 2 seconds of cumulative licking time to the drinking nozzle. The evaluation of this experiment was carried out using the number of the electric shocks. Results are shown in Fig. 1.

[0068]

Symbols # and ## in Fig.1 show that, when a significant difference test was carried out by Dunnett test, $p<0.05$ and $p<0.01$ represent that there is a significant difference in comparison with the control group treated with saline containing 0.1 % bovine serum albumin.

As apparent from the results shown in Fig. 1, the number of times of drinking water was dose-dependently, significantly decreased by the intracerebroventricular administrations of α-MSH and MTII in comparison with the control group.

[0069]

Experiment 3

Anti-anxiety action of Compound 4 in Table 1 in Vogel test (Conflict test) in rats was studied.

Male SD rats weighing 220 to 240 g (Charles River Japan Inc.) were used. Rats deprived of drinking water for 48 hours were divided into 10 animals for each group. To rats of group to be administered with the test compound was subcutaneously administered the test compound which was prepared by dissolving a predetermined amount of Compound 4 in Table 1 in saline for injection and adding 0.5 M aqueous sodium hydroxide solution to adjust to pH 4 - 5. Thirty minutes after the administration, rats were placed in a apparatus for the test, and drinking behaviors during the time of free access to drinking water for 3 minutes were measured. During the time of free access to drinking water, an electric shock (1.0 mA) was released, every 2 seconds of cumulative licking time to the drinking nozzle. The evaluation of this experiment was carried out using the number of the electric shocks. Results are shown in Fig. 2.

[0070]

Symbol ** in Fig. 2 shows that, when a significant difference test was carried out by Dunnett test, $p<0.01$ represents that there is a significant difference in comparison with the control group which

were not exposed to an electric shock to drinking nozzle. Symbol ## in Fig. 2 shows that, when a significant difference test was carried out by Dunnett test, $p<0.01$ represents that there is a significant difference in comparison with the group which were treated with an isotonic sodium chloride solution and exposed to electric shocks to drinking nozzle.

As apparent from the results shown in Fig. 2, the number of times of drinking water of the group exposed to an electric shock in comparison with the group which were not exposed to electric shocks. However, this decreased number of times of drinking water was significantly, dose-dependently antagonized by the subcutaneous administration of 1 mg/kg, 3 mg/kg or 10 mg/kg of Compound 4 in Table 1.

[0071]

Experiment 4

Anti-anxiety action of Compound 4 in Table 1 in forced swim stress-induced anxiety model of rats was studied.

Male SD rats weighing 220 to 240 g (Charles River Japan Inc.) were used. Rats were divided into 10 animals for each group. To rats of group to be administered with the test compound was subcutaneously administered the test compound which was prepared by dissolving a predetermined amount of the test drug in saline for injection and adding 0.5 M aqueous sodium

hydroxide solution to adjust to pH 4 - 5. Thirty minutes after the administration, rats were exposed to a forced swim stress by placing in a black cylinder (20 cm internal diameter, 40 cm high) containing 25 cm deep of water maintained at 25°C. Duration of the forced swim stress was 2 minutes, and the anti-anxiety action was studied by the elevated plus-maze test, which was carried out 5 minutes after the forced swim stress.

The elevated plus-maze used for the test consisted of open arms (10 cm wide, 50 cm long) and close arms (10 cm wide, 50 cm long), and the open arms and the enclosed arms were covered with 1 cm-high and 40 cm-high transparent Plexiglas, respectively. The plus-maze was placed in 50 cm high from the floor. Luminosity at the center of the maze was 40 lux. Each rat was placed in the center of the plus-maze facing one enclosed arm. The amount of time spent in open arms of the maze was recorded during a 5-minute period. Results are shown in Table 3.

[0072]

Symbol ** in Fig. 3 shows that, when a significant difference test was carried out by Dunnett test, $p<0.01$ represents that there is a significant difference in comparison with the control which is not exposed to the forced swim stress. Symbol ## in Fig. 3 shows that, when a significant difference test was carried out by Dunnett test, $p<0.01$ represents that

there is a significant difference in comparison with the group exposed to the forced swim stress by treating with saline.

As apparent from the results shown in Fig. 3, the amount of time spent in open arms of the group exposed to the forced swim stress is significantly decreased in comparison with the group which were not exposed to the forced swim stress. However, this decreased amount of time spent in open arms was significantly, dose-dependently antagonized by the subcutaneous administration of 0.3 mg/kg, 1 mg/kg or 3 mg/kg of Compound 4 in Table 1.

[0073]

Experiment 5

Anti-depressant action of Compound 4 in Table 1 in olfactory bulbectomized rats was studied.

Male SD rats weighing 220 to 240 g (Charles River Japan Inc.) were used. Rats were anesthetized with sodium pentobarbital, the olfactory bulbs were removed by suction using the metal pipe linked to a water aspirator. Two weeks after the removal of the olfactory bulbs, rats were divided into 10 or 11 animals for each group. To rats of group to be administered with the test drug was subcutaneously administered once a day for 2 weeks; the test drug which was prepared by dissolving a predetermined amount of Compound 4 in Table 1 in saline for injection and adding 0.5 M aqueous

sodium hydroxide solution to adjust to pH 4 - 5. Twenty four hours after the final administration, rats were placed in the center of a circular open field apparatus (70 cm diameter 25 blocks), and the number of crossings among blocks during 3 minutes was counted. Results are shown in Fig. 4.

[0074]

Symbol ** in Fig. 4 shows that, when a significant difference test was carried out by Dunnett test, $p<0.01$ represents that there is a significant difference in comparison with the control group of which olfactory bulbs were not removed. Symbol ## in Fig.4 shows that, when a significant difference test was carried out by Dunnett test, $p<0.01$ represents that there is a significant difference in comparison of the olfactory bulbectomized group, which were administered with saline.

[0075]

As apparent from the results shown in Fig. 3, the number of crossings among blocks in the open field of the olfactory bulbectomized rats was significantly increased in comparison with rats whose olfactory bulbs were not removed. However, the increased number of crossings among blocks in the open field was significantly, dose-dependently antagonized by the subcutaneous administration of 1 mg/kg, 3 mg/kg or 10 mg/kg of Compound 4 in Table 1.

[0076]

From the above results, the compounds, which antagonize MC_4 receptor are useful as therapeutic agents of depression or anxiety because of their inhibitory action of anxiogenic-like symptoms and depressive-like symptoms.

[0077]

[Brief Description of Drawings]

Fig. 1 shows the results of anxiogenic-like activity by Vogel test in rats in Experiment 2.

Fig. 2 shows the results of anti-anxiety activity by Vogel test in rats in Experiment 3.

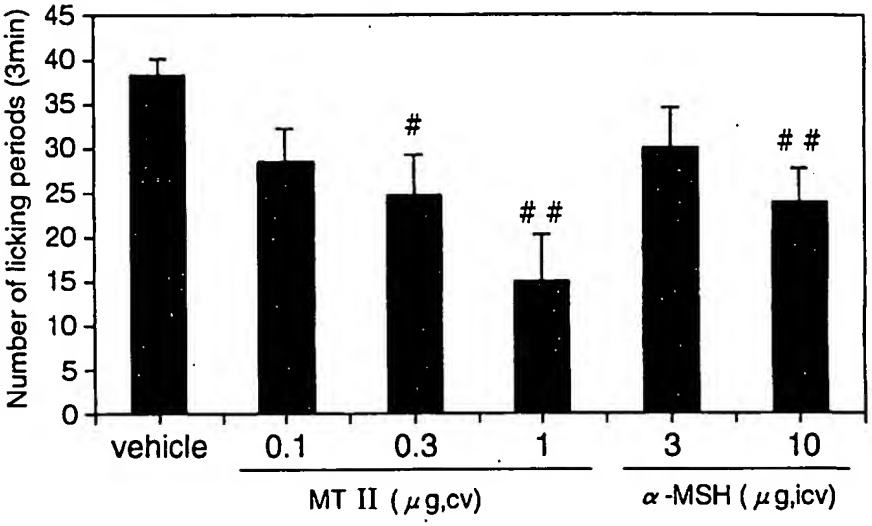
Fig. 3 shows the results of anti-anxiety activity in forced swim stress-induced anxiety model rats in Experiment 4.

Fig. 4 shows the results of anti-depression activity in olfactory bulbectomized rats in Experiment 5.

[Title of Document] Drawings

[Fig. 1]

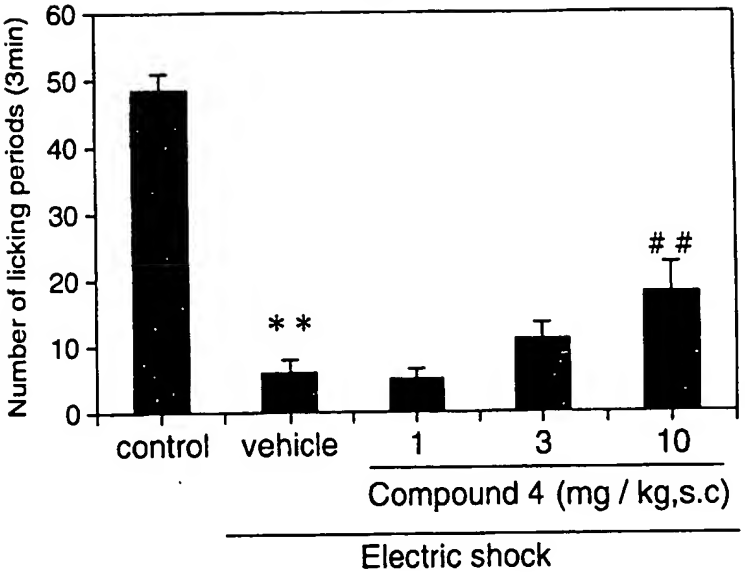
FIG. 1



N = 7~12 #: p<0.05; # #: p<0.01 vs vehicle

[Fig. 2]

FIG. 2

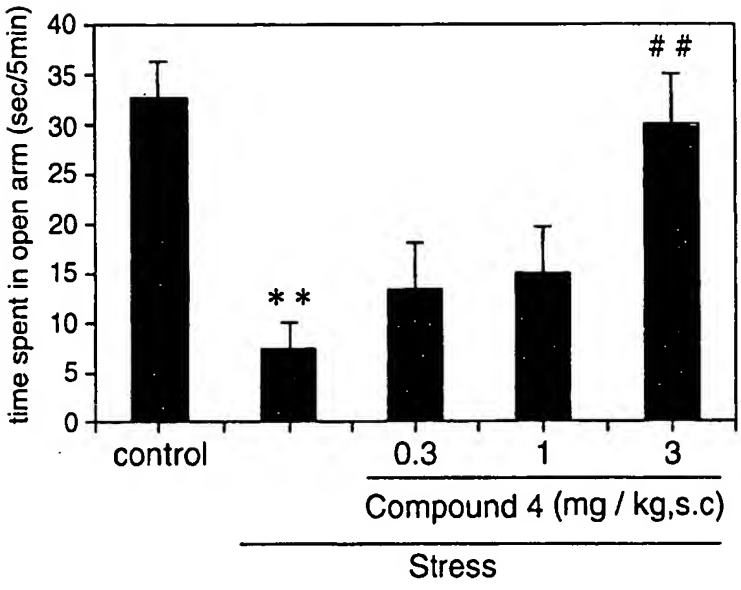


N = 10

* *: p<0.01 vs control
# #: p<0.01 vs vehicle

[Fig. 3]

FIG. 3

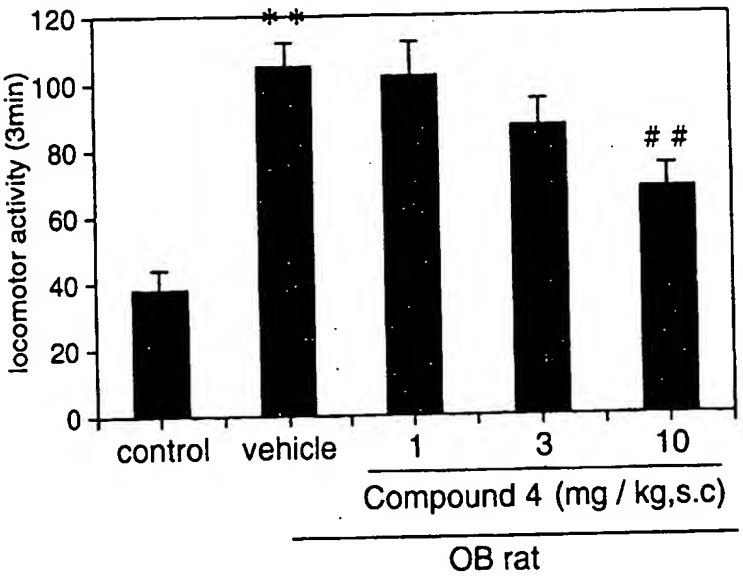


N = 10

* * : p<0.01 vs control
: p<0.01 vs vehicle

[Fig. 4]

FIG. 4



N = 10~11

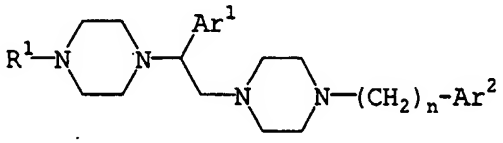
* *: p<0.01 vs control
# #: p<0.01 vs vehicle

[Title of Document] Abstract

[Problem] There is provided a pharmaceutical preparation for anxiety neurosis or depression.

[Solving Means] A therapeutic preparation for anxiety neurosis or depression which comprises a MC_4 receptor antagonist as an effective ingredient; and a piperazine derivative represented by Formula [1]:

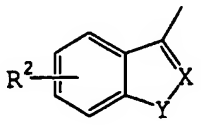
[Formula 15]



[1]

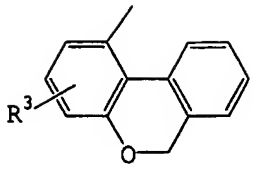
[wherein Ar^1 is a substituted or unsubstituted phenyl group, or a substituted or unsubstituted naphthyl group; Ar^2 is a substituted or unsubstituted naphthyl group, a quinolyl group, a group represented by the formula:

[Formula 16]



(wherein R^2 is a hydrogen atom or a halogen atom; and X-Y is C-NH, C-O, C-S or N-O) or a group represented by the formula:

[Formula 17]



(wherein R^3 is a hydrogen atom, a hydroxyl group or a C_{1-10} alkoxy group); R^1 is a hydrogen atom, a C_{1-10} alkyl group, a C_{3-10} alkenyl group, a phenyl group, a pyrimidin-2-yl group or an amidyl group; and n is an integer of from 1 to 10], or a pharmaceutically acceptable salt thereof.

[Selective Drawing] None